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September 11, 2017

Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Via https://www.regulations.gov/

Re: Docket No. FDA-2017-N-2903

Dear Food and Drug Administration:

These comments are submitted in response to the Federal Register Notice of a Public Workshop entitled 'Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting: A Scientific Discussion of Present and Future Capabilities', and the associated request for comments.

I write these comments as an expert on addiction, and the behavioral, cognitive, and central nervous system effects of drugs. I am also Vice President, Research, Health Policy, and Abuse Liability of the consulting firm Pinney Associates, Inc. We have extensive experience in advising both branded and generic pharmaceutical companies on the development and assessment of abuse-deterrent (AD) formulations of opioids including designing and developing protocols for *in vitro* assessment of abuse-deterrent drug formulations, developing abuse potential assessments for regulatory submission, and developing and executing postmarketing risk management plans and Risk Evaluation and Mitigation Strategies for controlled substances. These comments are my own and do not represent those of any company for which we provide or have provided consulting services. Additionally, these comments were not vetted with anyone outside of our company, nor did any outside organization compensate me for my time to prepare these comments.

First, I commend the Food and Drug Administration (FDA) for its efforts to convene such a timely, well-conceived, and very well-prepared workshop on the evaluation of abuse deterrent (AD) opioids for the treatment of pain. The external scientific advisors reflected a diverse range of relevant expertise and were clearly stimulated by the thought-provoking presentations of participating FDA staff. This meeting is also highly relevant to national efforts to address the opioid crisis and will hopefully contribute to the President's Commission on the Opioid Crisis.

I believe the presentations and discussion raised several issues about the role of AD opioids, how to design and implement informative surveillance, as well as how to support effective communications and avoid miscommunications in order to support public policy. I address each of these in turn below.

The goals for AD opioids and potential outcomes for surveillance.

First, as I mentioned at the meeting, I would like to reiterate one of the opening comments by Dr. Sid Scholl, who was among the external experts on the Workshop panel. This was in response to the opening presentations by FDA which emphasized the importance of developing best practices for a broad range of potential outcomes including drug exposures, misuse, abuse, addiction, overdose, mortality, prevention, and more. As Dr. Schnoll pointed out, these are all important from a public health perspective, but they go far beyond what AD opioids were conceived, designed, or intended to achieve, as is evident from the more than 15 years of discussion by FDA with sponsors, in public hearings and in the draft and final guidance documents. We need to distinguish the overall public health goals of preventing and reducing opioid abuse, addiction, and overdose in America, which can only be achieved by broad comprehensive demand and supply reduction efforts, from the important but relatively narrow and specific contribution of AD opioids, and not expect that AD opioids are going to address all of these problems by themselves. They can't, and their effectiveness and value to comprehensive opioid control efforts must be evaluated by measures that are appropriate to what they are designed to do.

As stated in FDA's 2015 Guidance (Abuse-Deterrent Opioids – Evaluation and Labeling, heretofore in my comment the "AD Guidance"): "One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse." (page 1-2), they are defined by "properties shown to meaningfully **deter** abuse even if they do not fully **prevent** abuse." [bold in original] (page 2). More specifically, as described in the guidance which describes laboratory and clinical studies to evaluate these properties, they are designed to deter or resist or increase the effort to be tampered or defeated so as to enable more rapid absorption by the oral route, nasal insufflation, smoking, and injection use. Going forward we need to be careful to distinguish surveillance designed to evaluate how well AD opioids are working to achieve the goals that they are designed to do, product by product, and label by label, e.g., "has physicochemical properties expected to make abuse by injection difficult…[and]… are expected to reduce abuse via the intranasal route… [but] cannot be concluded… to reduce abuse via the oral route." It seems a reasonable goal for improved surveillance to determine if a product so-labeled actually deters injection and nasal abuse because if so, this is a potentially important public health outcome because the risks of abuse and overdose are likely greater when administration is by injection and nasal insufflation than by intact oral administration.

Distinguishing AD opioid molecules and formulations.
Initial presentations prompted questions about the ability of current data sources to distinguish AD molecules and formulations and how to improve them with best practices. These are important questions. However, there are two additional important distinctions that are presently not addressed adequately in surveillance, nor in many of the reports and public statements from federal agencies and some experts. Namely, (1) whether the drug was prescribed or not, and (2) whether a molecule or substance used, self-reported or identified was actually a licitly manufactured pharmaceutical or if it was contained in an illicitly manufactured counterfeit product. These are important distinctions because when they are not established, wrong conclusions by agencies, experts, and media reports to the public can be made. Furthermore, the potential solutions to abuse and overdose of licitly made opioids in prescribed patients are different from those involving abuse of illicit products by non-prescribed patients (as discussed by Scholten and Henningfield, 2015a,b; 2016a,b).

For example, some reports of opioid overdose present the data in two broad categories: (1) heroin, and (2) prescription by either stating or implying that opioids other than heroin represent prescription opioid abuse and overdose. This fuels media, public and policy maker misconceptions about the nature of the problem and the necessary solutions. In reality, illicit fentanyl and other synthetic opioids including street counterfeit products are no more "prescription opioids" than is heroin. Thus, it is not surprising to see media reports and statements by policy makers that the main opioid problem is "prescription opioids" and the main solution is to reduce prescribing. In reality, people with pain who are prescribed opioids are not the main problem or the main population at risk of abuse and overdose. Of course, we need better education, oversight and controls to minimize over-prescribing and inappropriate prescribing. At the same time, under-prescribing can create unnecessary suffering in people with pain without addressing opioid abuse and overdose (Koop, 2003, 2006, 2007; Scholten and Henningfield, 2016b). We need to develop our policies with recognition that most people who abuse opioids and die of opioid overdose were not prescribed patients, and most overdose deaths are due to heroin, and illicitly made and marketed fentanyl and other synthetic opioids, often in combination. The most draconian restrictions on prescribing will do little to reduce opioid abuse and overdose in these population but they will increase suffering, and such policies are likely to increase the disparities that already exist, whereby low income and minority persons and people without health insurance are already substantially less likely to be properly treated for their pain (Institute of Medicine, 2011).

Similarly, we see reports that "prescription opioids" have exceeded illicit opioids as the gateway to opioid abuse, addiction and overdose, again implying that opioid prescribing and people with pain are the problem. In fact, most people who report that their first opioids were prescription were likely not prescribed patients and their drug was most likely either an illicitly diverted product that was intended for prescription use, or counterfeit product, and data concerning the mix are likely inaccurate because people are notoriously inaccurate in their reports of what they used and in many cases (e.g., with counterfeit products) there is no way for them to know if the product was a "prescription opioid" or not.

With respect to approved AD opioids, they appear likely to represent an extremely small fraction of opioids first used by abusers, in part because they are less attractive and less valued targets (confirmed by surveys), and because their prescribing and market share is tiny compared to non-AD opioids. That makes tracking their impact particularly challenging for surveillance.

Assessing the benefits of AD opioids and their role in addressing the very serious problem of undertreated pain in America, as described by the Institute of Medicine in 2011 and continuing today, particularly in low income and minority populations. In principle, AD opioids should provide reassurance that those who warrant opioids for treatment of pain can be appropriately prescribed with reduced concerns that their medicines will cause harm or that they will be the targets of theft. Unfortunately, in part because some are new and because they cost more than their non-AD counterparts, AD opioids appear to be vastly under prescribed and are not displacing non-AD products to the extent that would be ideal from the perspectives of public health, as well as providing incentives for continuing AD medication development. I believe that we need to encourage insurance providers and state and federal agencies to increasingly prescribe

AD opioids in place of non-AD opioids. Some organizations have policies such as not prescribing AD opioids until a patient has had their medication stolen or other problems at least two times. The Veterans Administration representatives at earlier FDA AD opioid public meetings have stated that they do not see that the potential public health benefits of AD opioids justify their costs because, as they rightly note, their prescribed patients are at overall low risk of abuse and diversion. Such policies are not fostering the transformation of the opioid market from nonprotected non-AD products to AD products that seems vital in the long run.

The really big issue is how AD opioids fit into the bigger picture of addressing opioid abuse in America while also addressing inappropriately and undertreated pain. Especially tragic is that undertreatment of pain and blunt instrument approaches to addressing opioid abuse hurt low income and minority people the most. Draconian restrictions on prescribing, one-week limits on prescriptions, and inappropriate burdens on prescribers especially hurt low income, minority and disenfranchised populations. Pain is best and most safely treated by comprehensive pain management approaches. Perhaps nowhere has this been better documented than in certain military settings that have evaluated comprehensive multimodal pain management that includes opioids (e.g., Vallerand, Cosler, Henningfield, and Galassini, 2015).

Overview of the place of AD opioids and FDA's efforts in addressing opioid abuse and overdose in the United States.

It is encouraging that this workshop brought together representatives from FDA, Centers for Disease Control and Prevention (CDC), National Institute on Drug Abuse (NIDA), National Cancer Institute (NCI), National Center for Health Statistics (NCHS), the Substance Abuse and Mental Health Services Administration (SAMHSA), and other organizations, though there are still other stakeholders and organizations that need to be included going forward. We need more such collaborations as exemplified by apparently accelerating collaborations between NIH and FDA as discussed in the 2017 *New England Journal of Medicine* article by NIDA director Dr. Nora Volkow and NIH director Dr. Francis Collins. These two days have brought several key agencies together, educating, listening, and learning. I hope you go forward working ever more closely because we need better cross-agency coordination in counting and reporting. We should not be counting illicitly made and marketed fentanyl and other synthetics as prescription drugs, nor conflating opioid prescribed patients (who are not the main problem), with nonpatients who reported use of prescription drugs as their gateways. Hopefully interagency discussions with increased external expert input will lead to better surveillance and more accurate public communications.

The FDA and AD opioids cannot address the opioid crisis alone. FDA's efforts and AD opioids do address some problems but not others. AD opioid efforts must be coordinated with other drug control efforts. An inconvenient truth is that part of the evidence that AD opioids are working is that there has been and will be migration by some of those who abuse prescription opioids to illicit synthetic opioids and heroin. Other interventions, including treatment on demand are critical to address that unintended consequence. Just about everyone with an opioid problem at some point asks for help. They should be given help as immediately and fully as if they had suffered a heart attack or auto accident, and not put on a waiting list if they don't have money or insurance. Some populations such as pregnant women who abuse opioids are another such population. Threatening them with jail does not help. But real help does help. Their access to

prenatal treatment is as important as their access to addiction treatment and both combined yield the best outcomes.

AD opioids should also be considered among harm reduction approaches for those who use opioids. More conventionally thought of harm reduction approaches to substance use related efforts to reduce disease and death include syringe or needle exchange programs (SEPs and NEPS, respectively), naloxone and perhaps in the near future naltrexone administration devices, medication assisted treatment for addiction, and condoms. Any one of these programs can be demonstrated to reduce risks and contribute to public safety, but all of these combined with comprehensive demand reduction efforts will most rapidly and dramatically lead our nation out of the opioid crisis.

Thus, a far better balance of demand and supply reduction efforts are vital, and these should be especially designed and supported to help those who need help the most and for whom treatment is out of reach because they are unable to pay, do not have adequate (or any) insurance and/or because there is no adequate treatment near where they live. Former Surgeon General C. Everett Koop repeatedly pointed out that it is "easy to get addictive drugs, but it is difficult for most folks who need it to get treatment" and that our nation must reverse this. (Koop, page 3, 2007; see also Koop, 2006, and Henningfield, Santora and Bickel, 2007). AD opioids must be viewed and integrated into such comprehensive efforts to prevent, reduce, and treat substance abuse and addiction (Schnoll and Henningfield, 2016; see also Scholten and Henningfield, 2016b). They cannot stand alone in this complex public health problem. NIDA, the College on Problems of Drug Dependence, and the American Society of Addiction Medicine, and other organization have articulated comprehensive approaches that need to be implemented.

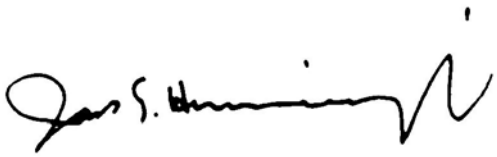
We need to track whether insurance providers and the Veterans Administration and other organization are paying for innovations in medicines including AD opioids. If they are not, innovations will sit on the shelf and willingness of potential developers to commit the considerable resources to such developments will diminish.

CDC's top 10 public health advances of the 20th century provide models: All involved comprehensive efforts, including technological innovations and education (CDC, 2013). For example, automobile safety, with seatbelts and safety glass eventually mandated for all cars, was supported by education and better highway systems. Infectious disease control involved new medicines, along with education to wash your hands, cover your nose when you sneeze, condom use, and more recently clean needle exchange. All ten advances involved surveillance to guide further regulation and identify adjustments in approaches.

Finally, I hope you will have input into the report being developed by the President's Commission on the Opioid Crisis. I hope that report reflects the importance of incentivizing new generations of medicines including AD opioids, so that the most risky and unprotected medicines eventually go the way of cars without seatbelts. But that can only happen with acceleration of efforts that we are addressing today. As with the public health advances of the 20th century, surveillance is vital to track the consequences of national efforts, intended and non-intended, and thereby guide corrections in course and the surprises that history shows should come as no surprise.

I appreciate the Food and Drug Administration's effort to advance the development of methods to support Category 4 labeling of AD opioid formulations. Thank you very much for the opportunity to provide these comments. Please contact me at PinneyAssociates at jhenning@pinneyassociates.com or 240-754-9053 if you have any questions or need further information.

Sincerely,



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